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FROM PENICILLIN TO PENEM AND CARBAPENEM. 1.

RACEMIZATION OF 6,6-DIBROMO SECOPENICILLIN, AND SYNTHESIS OF 2-OXO PENAM DERIVATIVE

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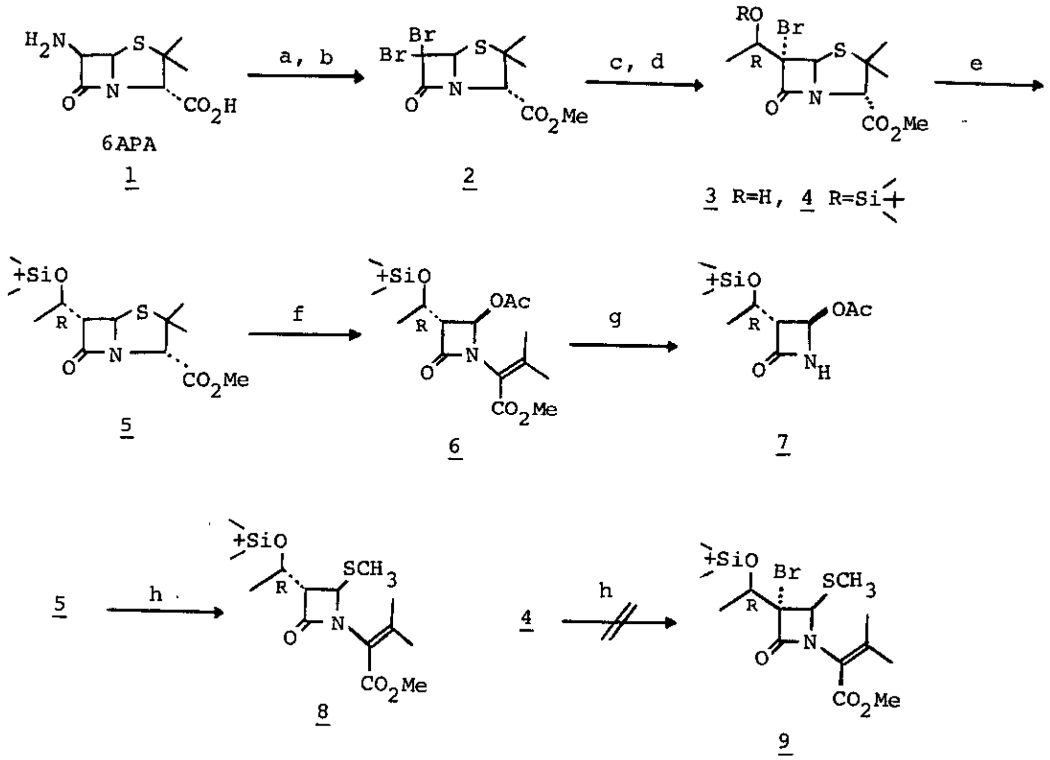
Abstract --- From 6-APA the azetidinone derivative (7) which has (R)-hydroxyethyl substituent at C-6 was prepared effectively. From dibromoseco derivative (10) the same type of compounds, 17 and 18 which has (S) type substituent were prepared, however these were proved to be optically inactive *dl*-form. Racemization occurred during the process of the formation of the secopenicillin (10) with excess CH_3I and 2.5 eq. of NaH or KO^tBu in THF via the acyliminium intermediate [22]. The 2-oxo penam derivative (27) was prepared from 17 as shown in Fig. 4.

After the discovery of thienamycin$^{1)}$, and the pioneering work of the syntheses of penem derivatives by Woodward and co-workers$^{2)}$, many efforts have been focused on the synthesis and the structure-activity relationship of the above antibiotics. Our current interest in these antibiotics prompted us to describe here some of our preliminary results of the degradation work of penicillin and the synthesis of 2-oxo penam derivative$^{3)}$.

In 1976 Merck chemists reported the introduction of the (R)-hydroxyethyl substituent at the C-6 position of benzyl 6,6-dibromopenicillanate$^{4)}$. At the beginning of the work we followed the same reaction using methyl 6,6-dibromopenicillanate (2), and found that the desired product 3, which had hydroxyethyl group of (R)-configuration at the C-6 position of the penicillin nucleus, was very easily obtained as crystal, mp 102°C. After protection of the hydroxy group by *tert*-butyldimethylsilyl chloride and imidazole the brom atom of the product (4), mp 54°C, was removed reductively using Zn powder in methanol in the presence of 2 eq. of acetic acid to give methyl 6α-[(R)-1'-*tert*-butyldimethylsilyloxyethyl]-penicillanate (5), NMR (60 MHz)($CDCl_3$) δ : 3.80 (1H, dd, J=5 and 1.5 Hz, C_6-H), 5.16 (1H, d, J=1.5 Hz, C_5-H).



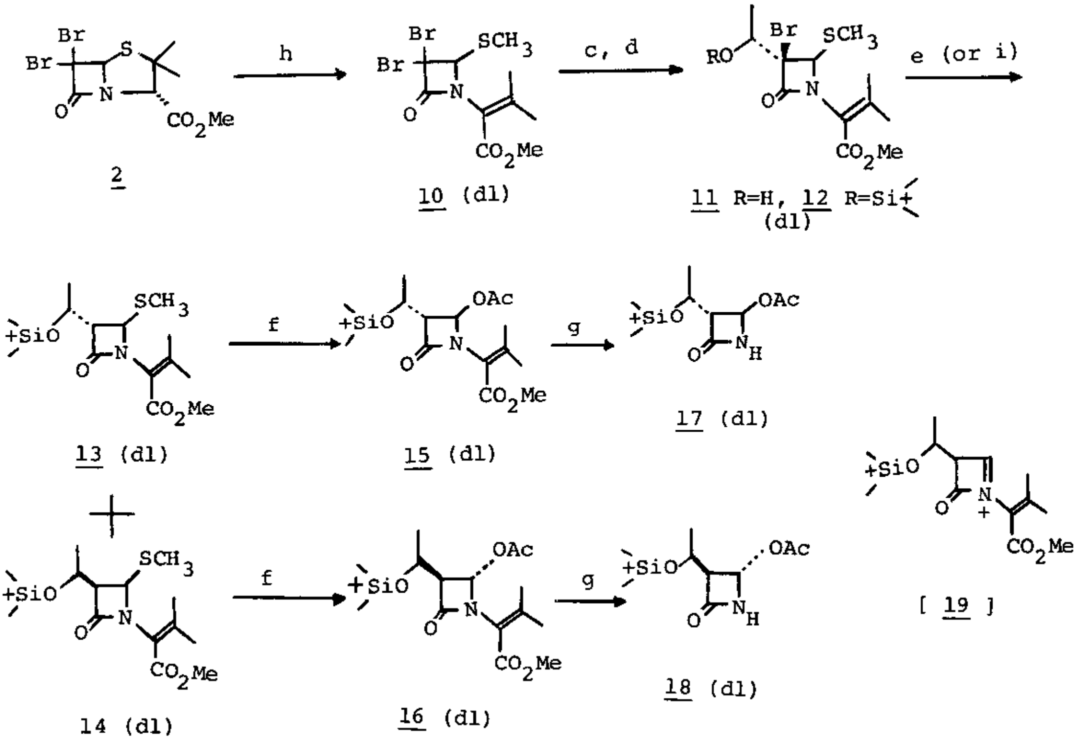
a, $NaNO_2/Br_2$; b, CH_2N_2 ; c, MeMgBr, CH_3CHO, -60°C; d, $^tBuMe_2SiCl$, imidazole, 55°C, 5 hr; e, Zn, 2 eq.AcOH/ MeOH ; f, $Hg(OAc)_2$/ AcOH, 90°C, 2 hr ; g, $KMnO_4$/ Acetone:H_2O(4:1) ; h, 7.5 eq. CH_3I, 2.5 eq. NaH (or KO^tBu)/ THF

Fig. 1

The conversion of 5 to the monocyclic β-lactam (6) which has an acetoxy group at the C-4 position of azetidinone ring was effectively achieved by heating 5 with 2 eq. of $Hg(OAc)_2$ in acetic acid (90°C) for 2 hr$^{5)}$ to give exclusively 3,4-*trans*-azetidinone (6), whose side chain at N-1 position was oxidatively removed (1.5 eq. $KMnO_4$ in aqueous acetone for 24 hr at 25°C)$^{5)}$ to afford the desired monocyclic β-lactam (7), mp 104°C, $[\alpha]_D^{20}$ +48°, identical with the standard sample previously prepared by Oida$^{6)}$. Monocyclic β-lactam (7) : NMR ($CDCl_3$) δ : 0.08 (CH_3 x 2), 0.84 (^{t}Bu), 1.19 (CH_3, d, J=6 Hz), 2.01 (OAc), 3.04 (1H, dd, J=4 and 1.5 Hz), 4.12 (1H, m), 5.75 (1H, d, J=1.5 Hz), 6.73 (NH).

During the study of the reactivity of the compound 5 an interesting reactivity difference between 4 and 5 was found. Namely the thiazolidine ring in 5 was cleaved within 5 min by treating with CH_3I / NaH or KO^tBu at room temperature to the seco derivative (8) cleanly, but the compound 4 which has Br atom instead of H in 5 was stable enough not to give seco derivative (9) even in prolonged reaction time. Presumably the steric effect by the substituents at C-6 prevented the attack of CH_3I to the S atom in 4 to give the seco derivative (9).

From the aspect of the stereochemistry it is interesting to know th difference of the reactivity between the dibromopenicillanate (2) and the seco-one (10) towards Grignard reagent (MeMgBr) to generate the hydroxyethyl moiety. At first dibromo seco derivative (10)7)was prepared from 2 by adding NaH (2.5 eq.) or KO^tBu (2.5 eq.) to a solution of 2 with 7.5 eq. of CH_3I in THF at room temperature. The progress of the reaction was monitored by silica-gel TLC (seco derivative (10): Rf = 0.3, benzene)8). After the reaction completed (



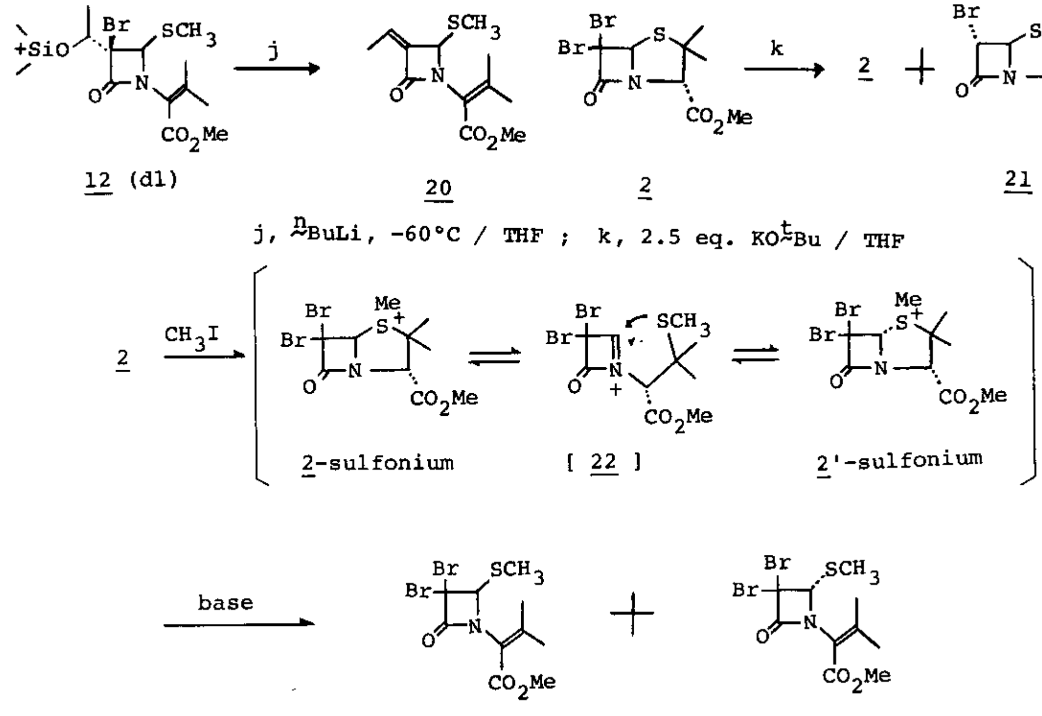
h, 7.5 eq. CH_3I, 2.5 eq. NaH (or KO^tBu) ; i, $^nBu_3SnH$, cat. cat. AIBN / C_6H_6, 65°C

Fig.2

usually 4-20 hr) the product 10 was purified by chromatography. The introduction of the hydroxyethyl group to the 3-position of the azetidinone molecule was performed analogously by the procedure for the preparation of 3 from 2. The hydroxyethyl group was introduced in 10 in 76 % isolated yield after chromatography. The brom atom of the silylated product (12), mp 68-69°C, was smoothly removed (Zn in MeOH in the presence of 2 eq. of acetic acid) to give a mixture of 3,4-*trans* and *cis* azetidinone derivative, 13 and 14 in a ratio of 62 : 38 in 50 % isolated yield. The assignment of the *trans* and *cis* configuration was deduced from the coupling constants between C_3-H and C_4-H, J=3 Hz in 13 and J=5.5 Hz in 14 respectively. These two compounds were easily separated on preparative TLC$^{8)}$, 13 : Rf = 0.48, and 14 : Rf = 0.32 (benzene : ethyl acetate = 10 : 1). On the other hand debromination using 2 eq. of ^{n}Bu$_3$SnH and catalytic amount of AIBN at 65°C in benzene gave the same products 13 and 14 in a ratio of 70 : 30 in 80 % isolated yield. Each separated products 13 and 14 gave 3,4-*trans* compounds 15 and 16 by treating with $Hg(OAc)_2$ in acetic acid. These results mean that the acyliminium intermediate [19] was attacked by the acetoxy anion to generate the sterically less-hindered 3,4-*trans* product 15 and 16 respectively. The substituent at N-1 of 15 was oxidatively removed by $KMnO_4$ to give the azetidinone derivative 17, mp 78°C. The comparison of the NMR of the standard 7 and 17 revealed that 17 had the (S)-configurated hydroxyethyl substituent at C-3 position as depicted in 17. 17 : NMR ($CDCl_3$) δ : 0.08 (CH_3x2), 0.84 (^{t}Bu), 1.26 (CH_2, d, J=6.5 Hz), 2.02 (OAc), 3.07 (1H, dd, J=4 and 1.5 Hz), 4.13 (1H, m), 5.61 (1H, d, J=1.5 Hz), 6.9 (NH). By the same reaction compound 16 gave the corresponding product 18, mp 75°C, which showed identical NMR of compound 7. Furthermore to confirm the configuration compound 12 was treated with *n*-Buli in THF at -60°C to give compound 20, whose NMR showed CH_3 doublet (J=7 Hz) at 2.0 ppm in $CDCl_3$. The foregoing results indicated that the dibromo secopenicillanate (10) which had no thiazolidine ring fused to the β-lactam ring yielded mainly α-orientated hydroxyethyl product (as depicted in 11) with S-type configuration.

At this stage we measured the $[\alpha]_D$ values of 11, 12, and 17 in $CHCl_3$. To our surprise they did not show any of the value ! We checked the blank test with the dibromo compound (2), $[\alpha]_D^{20}$ +190° (c 1.27, $CHCl_3$) by treating with KO^{t}Bu (2.5 eq.) in THF, and got a 1:1 mixture of 2 and monobromo compound 21,

$[\alpha]_D^{20}$ +157° (c 1.23, $CHCl_3$). By the same reaction in the presence of 7.5 eq. of CH_3I the seco derivative (10), which showed $[\alpha]_D^{20}$ +18.3°, was obtained after TLC separation. In case of using NaH the sample of seco derivative (10) which had $[\alpha]_D^{20}$ +7.5° was obtained and this value was reduced to +4.6° after one more



12 (dl) 20 2 21

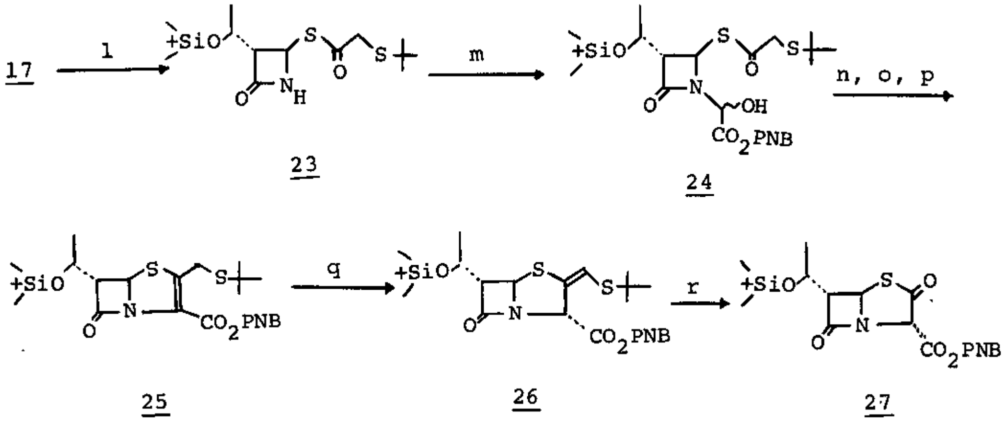
j, ^{n}BuLi, -60°C / THF ; k, 2.5 eq. KO^{t}Bu / THF

10 (dl)

Fig.3

TLC purification. On silica-gel TLC the seco derivative (10) and the monobromopenicillanate (21) showed almost the same Rf value (0.3, benzene), but the NMR of the isolated seco derivative, $[\alpha]_D$ +18.3°, cleanly showed that this sample was contaminated with about 11 % of monobromopenicillanate (21) which corresponded to the above value of +18.3°. The situation was the same for the sample of seco derivative of $[\alpha]_D$ +7.5° (about 4 % contaminated with 21). By the above results it is reasonably concluded that the racemization occurred during the process of the formation of the seco product 10, and the process was interpreted by the analogous mechanism which included the acyliminium intermediate [22] proposed by Denerley and Thomas$^{9)}$. Because of the almost same possibility to attack the acyliminium intermediate [22] by intramolecular sulfide a 1:1 mixture of 2- and 2'- sulfonium should be formed, and by the result of which dibromo seco compound (10) was formed as a dl form (Fig. 3).

With the important material (17) in hand we tried to get the 2-oxo penam derivative (27)$^{3)}$. Displacement of the acetoxy group in 17 was effected by reaction with 1.1 eq. of sodium *t*-butylthio-thioacetate to afford 23. The azetidinone derivative (23) was then coupled with *p*-nitrobenzylglyoxylate in refluxing benzene to give the aminal (24)$^{2)}$, which was chlorinated with thionyl chloride and 2,6-lutidine, and then the ylide was formed successfully with triphenyl phosphine and pyridine. The intramolecular Wittig reaction in toluene at 90°C in the presence of catalytic amount of hydroquinone for 5 hr gave the expected penem derivative (25), mp 107°C, NMR ($CDCl_3$) δ : 4.12 and 3.84 (2H, AB quartet, J=15.5 Hz, $-C\underline{H}_2S{+}$). The crucial step for the isomerization of the double bond to the exo-one was performed satisfactorily with one equivalent of triethylamine in CH_2Cl_2 at room temperature for 1 hr to afford the penam derivative (26), mp 117°C, NMR ($CDCl_3$) δ : 5.18 (1H, C_3-H) and 6.22 (1H, $=C\underline{H}S{+}$), and then by ozonolysis in CH_2Cl_2 at -40°C the desired *p*-nitrobenzyl-(6, 1')-*erythro*-5,6-*trans*-6-(1'-*t*-butyldimethylsilyloxyethyl)-2-oxo-penam-3-carboxylate (27) was obtained smoothly. Rf = 0.55 (benzene : ethyl acetate = 5 : 1). NMR ($CDCl_3$) δ : 0.09 ($CH_3 \times 2$), 0.85 (^{t}Bu), 1.36 (CH_3, d., J=6 Hz), 3.56 (1H, dd, J=4 and 2 Hz), 5.06 (1H, s), 5.28 (2H, s), 5.40 (1H, d , J=2 Hz), 7.4-8.4 (4H). IR ν (liq.) cm^{-1}: 1798, 1763, 1730, 1610, 1522.



l, $NaSCOCH_2S^tBu$/ dioxane:H_2O; m, $CHOCO_2PNB$ / C_6H_6 ; n, $SOCl_2$/THF:dioxane, -10°C ; o, $P(C_6H_5)_3$/py./ dioxane:DMF (4:1), 70-80°C, 3hr ; p, toluene, 90°C, 5 hr ; q, NEt_3/ CH_2Cl_2 ; r, O_3, MeSMe

Fig. 4

PNB : p-nitrobenzyl

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